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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/600,201	SLEPNEV, VLADIMIR I.	
	Examiner	Art Unit	
	Angela M. Bertagna	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18,19,21-35,37-49,62,63 and 65-75* is/are pending in the application.

4a) Of the above claim(s) *74 and 75* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18,19,21-35,37-49,62,63 and 65-73* is/are rejected.

7)☒ Claim(s) *18,22-24,34,38-40,62,63 and 66-68* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/18/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. Applicant's response filed on May 12, 2009 is acknowledged. Claims 18, 19, 21-35, 37-49, 62, 63, and 65-75 are currently pending. In the response, Applicant amended claims 18, 34, 37, 38, 43, 62, 63, 66, and 70. Claims 74 and 75 remain withdrawn from consideration as being drawn to a non-elected invention.

Applicant's amendments to the claims have overcome all of the previously made objections and rejections, and therefore, they have been withdrawn. The following are new grounds of rejection. Since the new grounds of rejection were necessitated by Applicant's amendment, this Office Action is made **FINAL**.

Information Disclosure Statement

2. Applicant's submission of an Information Disclosure Statement on November 18, 2008 is acknowledged. A signed copy is enclosed.

Claim Objections

3. Claim 18 is objected to because of the following informalities: Replacing the term "said multiplex amplification reaction" in step (b) with "said multiplex amplification regimen" is suggested to maintain consistency within the claim. Also, replacing the terms "said set of polymorphic sites" and "the set of target polymorphic sites" in step (c) with "said set of known polymorphic sites" is suggested to maintain consistency within the claim.

Claims 22-24 are objected to because of the following informalities: Replacing the term "said amplification regimen" in claims 22-23 and the term "said regimen" in claim 24 "with "said multiplex amplification regimen" is suggested to maintain consistency with claim 18.

Claim 34 is objected to because of the following informalities: Replacing the terms "said set of polymorphic sites" and "the set of target polymorphic sites" in step (c) with "said set of known polymorphic sites" is suggested to maintain consistency within the claim.

Claims 38-40 are objected to because of the following informalities: Replacing the term "said amplification regimen" in claims 38-39 and the term "said regimen" in claim 40 "with "said multiplex amplification regimen" is suggested to maintain consistency with claim 34.

Claim 62 is objected to because of the following informalities: Replacing the term "said amplification regimen" in step (VII) with "said multiplex amplification regimen" is suggested to maintain consistency within the claim. Also, replacing the terms "said group of polymorphic sites" and "the set of target polymorphic sites" with "said group of known polymorphic sites" is suggested to maintain consistency within the claim. Also, the replacing phrase "distinctly sized amplification product" in step (a) with "plurality of distinctly sized amplification products" is suggested.

Claim 63 is objected to because of the following informalities: This claim appears to contain two periods at the end of the claim.

Claims 66-68 are objected to because of the following informalities: Replacing the term "said amplification regimen" in claims 66-67 and the term "said regimen" in claim 69 "with "said multiplex amplification regimen" is suggested to maintain consistency with claim 62.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 70 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 70 is indefinite, because there is insufficient antecedent basis for the terms "said first and/or second tag sequences".

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 18, 19, 21, 22, 26, 27, 34, 35, 37, 38, 42, and 43 are rejected under 35 U.S.C. 102(e) as being anticipated by Chen et al. (US 2003/0096277 A1; cited previously).

These claims are drawn to an amplification-based method of determining the identities of the nucleotides at a set of known polymorphic sites.

Regarding claims 18 and 34, Chen teaches a method of determining, for a given nucleic acid sample, the identities of the nucleotides at a set of known polymorphic sites to be interrogated, comprising:

(a) subjecting to a multiplex amplification regimen, a population of primer extension products generated from a nucleic acid sample, wherein each primer extension product comprises a member of a set of tag sequences that specifically corresponds to the presence of one specific nucleotide at a member of the set of known polymorphic sites and also a first tag sequence (see, for example, paragraphs 19, 27, 31-52, 68-72, 87-89, 103-105, and Table 1, where the designations upstream, forward, reverse, and downstream are arbitrary; see also Figures 1-2), and

wherein the multiplex amplification regimen is performed using one upstream amplification primer for each sequence comprising a known polymorphic site to be interrogated and a set of distinguishably labeled downstream amplification primers that each comprise a tag sequence comprised by a member of the population of primer extension products and a distinguishable label that specifically corresponds to the presence of a specific nucleotide at the polymorphic site and wherein the upstream amplification primers are selected such that each polymorphic site of the set of known polymorphic sites to be interrogated corresponds to a distinctly sized amplification product (see, for example, paragraphs 19, 27, 31-52, 68-72, 87-89, 103-105, and Table 1; see also Figures 1-2),

(b) separating distinctly sized amplification products produced by the multiplex amplification reaction by size and/or charge (see, for example, paragraphs 27, 49-51, 62-63, 75, and 105), and

(c) detecting the incorporation of a distinguishable label in a plurality of distinctly sized amplification products, thereby determining the identity of the nucleotide at each member of the set of known polymorphic sites, wherein the same set of distinguishably labeled primers determines the identities of the nucleotides at all members of the set of target polymorphic sites (see, for example, paragraphs 27, 49-51, 62-63, 75, and 105; see also Table 1).

Further regarding claim 34, Chen teaches that the primer extension products also contain a common tail sequence that is located at a distinct distance 5' of the polymorphic site, relative to the distance of the common tail sequence from a polymorphic site on molecules in the sample containing other polymorphic sites and conducting the multiplex amplification reaction using an upstream primer comprising the common tail sequence (see, for example, paragraphs 55 and 57). Chen further teaches selecting the upstream primers such that each polymorphic site in the set of polymorphic sites corresponds to a distinctly sized amplification product (paragraphs 55 and 57).

Regarding claims 19 and 35, Chen teaches that the distinguishable label is a fluorescent label (see paragraphs 58 and 63, for example; see also Table 1).

Regarding claims 21 and 37, Chen teaches that the separation method is capillary electrophoresis (paragraphs 62-63, for example).

Regarding claims 22 and 38, the amplification regimen conducted in the method of Chen comprises at least two amplification reaction cycles, with each cycle comprising the steps of: 1) nucleic acid strand separation; 2) oligonucleotide primer annealing; and 3) polymerase-mediated extension of annealed primers (see, for example, paragraph 72).

Regarding claims 26 and 42, Chen teaches a modular apparatus comprising a thermal cycling device, a sampling device, a capillary electrophoresis device, and a fluorescence detector

(see, for example, paragraphs 72-75). It is noted that neither the claims nor an explicit definition in the specification requires the elements of the modular apparatus to be physically connected to one another.

Regarding claims 27 and 43, Chen teaches that the tag sequence has a length within the claimed range (see Table 1).

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 23-25 and 39-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (US 2003/0096277 A1; cited previously) in view of Woolley et al. (Analytical Chemistry (1996) 68: 4081-4086; cited previously).

Chen teaches the methods of claims 18, 19, 21, 22, 26, 27, 34, 35, 37, 38, 42, and 43, as discussed above.

Chen does not teach analyzing an aliquot of the PCR after each reaction cycle by capillary electrophoresis as required by claims 23, 24, 39, and 40.

Regarding claims 25 and 41, Chen teaches separation by capillary electrophoresis (see paragraphs 62-63, for example).

Woolley teaches a method for conducting PCR amplification and capillary electrophoresis in a microfabricated DNA analysis device (see abstract and pages 4082-4084).

Regarding claims 23-25 and 39-41, Woolley teaches taking an aliquot after 15, 20, 25, and 30 cycles of a PCR reaction and analyzing the amount of accumulating product by capillary electrophoresis with fluorescence detection to obtain real-time monitoring of product accumulation (see page 4085 and also Figure 5). Woolley also teaches that the disclosed integrated PCR-CE microdevices permit very rapid thermal cycling and electrophoretic separation, are suitable for use in virtually any other amplification method, permit less expensive real-time monitoring of product accumulation, and eliminate the need for sample handling between the amplification and capillary electrophoresis steps, thereby simplifying the process, eliminating pipetting errors, and reducing contamination opportunities (page 4086, column 2).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to utilize the integrated PCR-CE microdevice taught by Woolley when practicing the methods disclosed by Chen. An ordinary artisan would have been motivated to do so, since Woolley taught that the integrated PCR-CE microdevices permit very rapid thermal cycling and electrophoretic separation, are suitable for use in virtually any other amplification method, permit less expensive real-time monitoring of product accumulation, and eliminate the need for sample handling between the amplification and capillary electrophoresis steps, thereby simplifying the process, eliminating pipetting errors, and reducing contamination opportunities (page 4086, column 2). An ordinary artisan also would have been motivated to monitor aliquots of the amplification reaction mixture in order to monitor product accumulation in real-time as suggested by Woolley (see page 4085 & Figure 5). Finally, regarding claims 24 and 40, an ordinary artisan would have recognized from the teachings of Woolley that the number of aliquots analyzed during an amplification reaction was a results-effective variable that should be

optimized by routine experimentation. As noted in MPEP 2144.05, it is *prima facie* obvious to optimize results-effective variables using routine experimentation in the absence of unexpected results. In this case, an ordinary artisan would have recognized that analyzing more aliquots (*e.g.* after each reaction cycle) would have improved the method resulting from the combined teachings of Chen and Woolley by providing more data points for analysis and a clearer picture of the exponential and plateau phases of the amplification process. Thus, the methods of claims 23-25 and 39-41 are *prima facie* obvious over Chen in view of Woolley.

9. Claims 28-33, 44-49, 62, 63, 65, 66, and 69-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (US 2003/0096277 A1; cited previously) in view of Nolan et al. (US 6,287,766 B1; cited previously).

Claims 28 and 44 are drawn to the methods of claims 18 and 34, respectively, wherein the method utilizes a set of downstream primers consisting of four primers, each with a different 3'-terminal nucleotide. Claims 29-33 and claims 45-49 are drawn to the methods of claims 18 and 34, respectively, wherein the method comprises removing primers not incorporated into the primer extension products via digestion with Exonuclease I. Claims 62, 63, 65, 66, and 70-73 are drawn to an amplification-based method of determining the identities of the nucleotides at a set of known polymorphic sites that incorporates elements of claims 18, 34, 29-33, and 45-49.

Chen teaches the methods of claims 18, 19, 21, 22, 26, 27, 34, 35, 37, 38, 42, and 43, as discussed above.

Regarding claim 62, Chen teaches a method of determining the identities of single nucleotides at a group of known polymorphic sites, comprising:

I) providing a nucleic acid sample comprising the group of known polymorphic site (see paragraphs 72 and 105, for example),

II) separating the strands of the nucleic acid sample and re-annealing in the presence of (see paragraphs 72 and 105; see also paragraphs 19, 27, 31-52, 55, 57, 68-72, 87-89, 103-105, Table 1, and Figures 1-2):

(a) a set of first oligonucleotide primers comprising a 3' region that hybridizes to a sequence at a known distance upstream of a known polymorphic site in the group of known polymorphic sites, wherein each member of the first set of oligonucleotide primers comprises a common sequence tag located 5' of the 3' region, and wherein the members of the first set of primers is selected such that a plurality of distinctly sized amplification products is generated for each polymorphic site in the group of known polymorphic sites (see above, and in particular, paragraphs 55 and 57 and Figure 2, where the set of reverse primers having a common sequence tag is taught. As noted above, the designations upstream, downstream, forward, and reverse are arbitrary depending on the choice of the reference strand) and

(b) a set of second oligonucleotide primers, each member of the set comprising: (i) a region that hybridizes 3' of and adjacent to a polymorphic site in the group of polymorphic sites, (ii) a variable 3' terminal nucleotide, wherein, when the member is hybridized to the known sequence, the 3' terminal nucleotide is opposite the polymorphic site, and wherein, if and only if the 3' terminal nucleotide is complementary to the nucleotide at the polymorphic site, the 3' terminal nucleotide base pairs with the nucleotide at the polymorphic site, and (iii) a tag sequence that corresponds to the

variable 3'-terminal nucleotide of (ii) with the tag sequence located 5' of region (i) on the member (see above, and in particular, Figure 2, paragraphs 31-52 and Table 1),

III) contacting the annealed oligonucleotides resulting from step (II) with a nucleic acid polymerase under conditions that permit the extension of an annealed oligonucleotide such that extension products are generated, wherein the primer extension product from the first oligonucleotide primer, when separated from its complement, can serve as a template for the synthesis of the extension product of a member of the set of second oligonucleotide primers and vice versa (see above, and in particular, paragraphs 31-52, 55, 57, 72, and 105),

IV) repeating the strand separating and contacting steps (*i.e.* steps (II) and (III)) twice, such that a population of nucleic acid molecules is generated that comprises both a sequence identical to or complementary to the first oligonucleotide and a sequence identical to or complementary to one of the members of the second set of oligonucleotides (see paragraphs 72 and 105, for example),

V) subjecting the population of nucleic acid molecules to a multiplex amplification regimen, wherein the amplification regimen is performed using an upstream amplification primer comprising the common sequence tag comprised by the first oligonucleotide primers and a set of distinguishably labeled downstream amplification primers comprising a tag comprised by a member of the set of second oligonucleotide primers and a distinguishable label (see paragraphs 72 and 105; see also paragraphs 19, 27, 31-52, 55, 57, 68-72, 87-89, 103-105, Table 1, and Figures 1-2),

VI) separating a plurality of distinctly sized amplification produced by size and/or charge (see paragraphs 62, 63, 75, and 105, for example), and

VII) detecting the incorporation of at least one distinguishable label in a plurality of distinctly sized amplification products, thereby determining the identity of the nucleotides present at each member of the set of known polymorphic sites, wherein the same set of distinguishably labeled primers determines the identities of the nucleotides at all members of the set of target polymorphic sites (see, for example, paragraphs 27, 49-51, 55, 57, 62-63, 75, and 105 and also Table 1).

Regarding claim 63, Chen teaches that the distinguishable label is a fluorescent label (see, for example, paragraphs 58 and 63 and also Table 1).

Regarding claim 65, Chen teaches that the separation method is capillary electrophoresis (paragraphs 62-63, for example).

Regarding claim 66, the amplification regimen conducted in the method of Chen comprises at least two amplification reaction cycles, with each cycle comprising the steps of: 1) nucleic acid strand separation; 2) oligonucleotide primer annealing; and 3) polymerase-mediated extension of annealed primers (see, for example, paragraph 72).

Regarding claim 69, Chen teaches a modular apparatus comprising a thermal cycling device, a sampling device, a capillary electrophoresis device, and a fluorescence detector (see, for example, paragraphs 72-75). It is noted that neither the claims nor an explicit definition in the specification requires the elements of the modular apparatus to be physically connected to one another.

Regarding claim 70, Chen teaches that the tag sequence has a length within the claimed range (see Table 1).

Regarding claim 72, Chen teaches that the region that hybridizes 3' of and adjacent to the polymorphic site comprises 10-30 nucleotides (see Table 1).

Chen does not teach exonuclease digestion to remove unextended primers as required by claims 29-33, 45-49, and 62. Also, regarding claims 28, 44, and 73, Chen does not teach using a set of downstream primers consisting of four primers, each with a different 3'-terminal nucleotide. Finally, regarding claim 71, Chen does not specify the length of the 3' region that hybridizes at a known distance upstream of the known polymorphic site.

Nolan teaches a method of identifying polymorphisms using flow cytometry.

Regarding claims 28, 44, and 73, the method taught by Nolan in Example 5 (column 7, lines 1-63) comprises an oligonucleotide ligation assay (OLA) followed by PCR amplification with an upstream primer and a set of downstream primers that may be fluorescently labeled (column 7, lines 11-50). Nolan teaches that the downstream primers each have a different 3'terminal nucleotide (column 7, lines 27-30) in order to identify the polymorphism in a single reaction.

Regarding claims 29-33, 45-49, and 62, Nolan teaches an embodiment wherein unincorporated primers from an initial amplification reaction are degraded using the heat labile Exonuclease I followed by polymerase extension, where the initial denaturation step destroys the activity of the exonuclease (see for example, column 5, line 60 – column 6, line 20). Nolan also teaches multiplex detection of mutations using multiple sets of primers (column 7, lines 60-63).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Nolan to the methods disclosed by Chen. An ordinary artisan would have recognized from the teachings of Nolan that not all polymorphic sites may be

genotyped using only one or two allele-specific downstream primers, and therefore, would have been motivated to utilize a subset of four downstream primers each with a different 3'terminus, in order to accurately type these polymorphisms. An ordinary artisan also would have been motivated by the teachings of Nolan to incorporate an exonuclease digestion step following the initial primer extension reaction with the allele-specific primers. An ordinary artisan would have recognized from the teachings of Nolan that incorporation of an exonuclease digestion step following the initial primer extension reaction would have improved the methods of Chen by eliminating the possibility of mispriming events. Finally, regarding claim 71, it would have been *prima facie* obvious for one of ordinary skill in the art to conduct routine experimentation to determine the optimal length of the 3' region that hybridizes at a known distance upstream of the known polymorphic site. An ordinary artisan would have recognized from the teachings of Chen that the length of the 3' region that hybridizes at a known distance upstream of the known polymorphic site was a results-effective variable, and therefore, would have been motivated to conduct routine experimentation to determine the optimal length of this sequence in order to maximize amplification efficiency, for example. An ordinary artisan would have had a reasonable expectation of success in conducting this routine experimentation. It is further noted that no evidence has been presented to suggest that unexpected results are associated with the claimed length range. Thus, the methods of claims 28-33, 44-49, 62, 63, 65, 66, and 69-73 are *prima facie* obvious over Chen in view of Nolan.

10. Claims 67 and 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (US 2003/0096277 A1; cited previously) in view of Nolan et al. (US 6,287,766 B1; cited previously) and further in view of Woolley et al. (Analytical Chemistry (1996) 68: 4081-4086; cited previously.

The combined teachings of Chen and Nolan result in the methods of claims 28-33, 44-49, 62, 63, 65, 66, and 69-73, as discussed above.

Regarding claims 67 and 68, Chen teaches a method of detecting point mutations using capillary electrophoresis and laser-induced fluorescence detection (see paragraphs 62-63, for example).

Neither Chen nor Nolan teaches analyzing an aliquot of the PCR after each reaction cycle by capillary electrophoresis as required by claims 67 and 68.

Woolley teaches a method for conducting PCR amplification and capillary electrophoresis in a microfabricated DNA analysis device (see abstract and pages 4082-4084).

Regarding claims 67 and 68, Woolley teaches taking an aliquot after 15, 20, 25, and 30 cycles of a PCR reaction and analyzing the amount of accumulating product by capillary electrophoresis with fluorescence detection to obtain real-time monitoring of product accumulation (see page 4085 and also Figure 5). Woolley also teaches that the disclosed integrated PCR-CE microdevices permit very rapid thermal cycling and electrophoretic separation, are suitable for use in virtually any other amplification method, permit less expensive real-time monitoring of product accumulation, and eliminate the need for sample handling between the amplification and capillary electrophoresis steps, thereby simplifying the process, eliminating pipetting errors, and reducing contamination opportunities (page 4086, column 2).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to utilize the integrated PCR-CE microdevice taught by Woolley when practicing the method resulting from the combined teachings of Chen and Nolan. An ordinary artisan would have been motivated to do so, since Woolley taught that the integrated PCR-CE microdevices permit very rapid thermal cycling and electrophoretic separation, are suitable for use in virtually any other amplification method, permit less expensive real-time monitoring of product accumulation, and eliminate the need for sample handling between the amplification and capillary electrophoresis steps, thereby simplifying the process, eliminating pipetting errors, and reducing contamination opportunities (page 4086, column 2). An ordinary artisan also would have been motivated to monitor aliquots of the amplification reaction mixture in order to monitor product accumulation in real-time as suggested by Woolley (see page 4085 & Figure 5). Finally, regarding claim 68, an ordinary artisan would have recognized from the teachings of Woolley that the number of aliquots analyzed during an amplification reaction was a results-effective variable that should be optimized by routine experimentation. As noted in MPEP 2144.05, it is *prima facie* obvious to optimize results-effective variables using routine experimentation in the absence of unexpected results. In this case, an ordinary artisan would have recognized that analyzing more aliquots (*e.g.* after each reaction cycle) would have improved the method resulting from the combined teachings of Chen, Nolan, and Woolley by providing more data points for analysis and a clearer picture of the exponential and plateau phases of the amplification process. Thus, the methods of claims 67 and 68 are *prima facie* obvious in view of the combined teachings of Chen, Nolan, and Woolley.

Response to Arguments

11. As noted above, all of the previously made objections and rejections have been withdrawn in view of Applicant's amendments to the claims. Accordingly, Applicant's arguments filed on May 12, 2009 have been considered, but they are moot in view of the new grounds of rejection presented above.

Conclusion

12. No claims are currently allowable.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Ronai (US 5,512,441) teaches a method comprising a first amplification step using primers having long tails that are not complementary to the target nucleic acid followed by a second amplification step using primers having short tails that hybridize to the long tails (see abstract and Figure 2).

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANGELA BERTAGNA whose telephone number is (571)272-8291. The examiner can normally be reached on M-F, 9- 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ANGELA BERTAGNA/
Examiner, Art Unit 1637

/GARY BENZION/
Supervisory Patent Examiner, Art Unit 1637